Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

**An open access, online journal • www.smw.ch**

**Viewpoint** | Published 16 April 2020 | doi:10.4414/smw.2020.20248
**Cite this as:** Swiss Med Wkly. 2020;150:w20248

# HLA studies in the context of coronavirus outbreaks

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The unique health situation that we humans are currently living in at the global scale due to the COVID-19 pandemic urges scientists to gain maximum understanding about the characteristics of the new SARS-CoV-2 coronavirus, the way it contaminates individuals, and the genetic and non-genetic factors that influence our susceptibility or protection to its too often severe consequences. Little is known at the moment about specific immune mechanisms that would work against SARS-CoV-2, although such knowledge is expected to play a vital role in the absence of efficient drugs and vaccines, as is the case today. In this context, a particular focus has to be given to the human leucocyte antigen (HLA) system that governs our adaptive immunity.

HLA genes are known to display the highest level of diversity of our genome, with thousands of different alleles reported nowadays, each allele being also a combination of multiple single nucleotide polymorphisms (SNPs). This unique level of polymorphism likely results from thousands of generations (since the emergence of modern humans) of HLA molecular evolution where natural selection favoured genetic variation, balancing selection in the form of heterozygous advantage (in its different versions) being the most widely accepted model. The idea of such a model is that heterozygous individuals would display a higher fitness than homozygotes in pathogen-rich environments, different HLA molecules assuming complementary abilities to present pathogen-derived peptides to T cells and elicit an immune response. The consequence of this kind of selection, at the population level, is that HLA allele frequency distributions are more even than expected under neutral evolution, most human populations displaying between 85% and 95% heterozygosity at each HLA locus.

The strength of heterozygous advantage as a diversifying selective force, although salutary for population health, has its drawbacks for immunogenetics research. Indeed, when multiple alleles display even and thus rather low frequencies in populations, such as for HLA, the identification of significant associations between peculiar alleles and diseases becomes very challenging unless such associations are very strong and specific. Statistical tests may have insufficient power, in particular when sample sizes are low; and in the case of HLA, multiple alleles may confer small additive risk or protection effects to the same pathogen with the consequence of hiding significant signals for each individual marker. This may partly explain, among other difficulties, why a number of HLA and disease association studies provide weak results, as discussed in our accompanying paper "A review of HLA allele and SNP associations to highly prevalent infectious diseases in human populations" published in *Swiss Medical Weekly* [1]. As this review article was written just before the outbreak of the COVID-19 pandemic, which was declared a public health emergency of international concern by the World Health Organization (WHO) in January 2020, it did not address coronavirus infections. This is the reason why we summarise below the main publications relating HLA to SARS.

To date, the outbreak of the SARS-CoV-2 pandemic is too young for association studies with HLA markers to be already published. We thus searched the literature for case-control studies on SARS-CoV-1 infections, which caused a sudden epidemic in 2002−2003 in East Asia. As both viruses belong to the same beta-coronavirus family and share a high level of genetic similarity (about 80%, in contrast to MERS-CoV which broke out in the Middle-East in 2012 and is ~50% similar to SARS-CoV-2), the present review might be a useful reference for further association studies on SARS-CoV-2.

## Case-control studies

The first (often taken as a reference) case-control study was performed in Taiwan by Lin et al. [2], who suggested that HLA-B*46:01, found to be very common in SARS-CoV-1 patients, was a susceptibility allele for the disease. Actually, the HLA-B*46:01 association was found significant, after correction for multiple tests, only when the severe cases of SARS-CoV-1 (n = 6) and not all patients (n = 33) were compared with the control group (101 high-risk non-infected healthcare workers), the main issue being the small sample size of the severe cases group. Other associations with HLA-B*54:01, HLA-B*39:01 and HLA-B*13:01 did not remain significant after correction for multiple tests. A year later, Ng et al. [3] compared the frequencies of HLA alleles in 90 SARS patients with frequencies estimated on 18,774 HLA class I and 250 HLA class II serologically typed Chinese bone-marrow donors from Hong Kong. This study did not confirm the associ-

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ation with HLA-B*46:01 suggested by Lin et al. [2]. Instead, it reported a significant increase of HLA-B*07:03 frequency and a significant decrease of HLA-DRB1*03:01 frequency in SARS patients. However, some years later the same authors did not confirm their previous results when analysing independent cohorts of 102 SARS patients and 108 SARS contacts with improved design and typing methods [4]. Moreover, their new observations of a higher HLA-DRB4*01:01:01:01 frequency in SARS-susceptible and higher HLA-B*15:02 and HLA-DRB3*03:01:01 frequencies in SARS-resistant subjects did not remained significant after correction for multiple tests. Yuan et al. [5] also compared Hong Kong Chinese SARS patients (n = 176) with unrelated Hong Kong Chinese bone marrow donors and found no significant differences in their HLA-A, HLA-B and HLA-DRB1 allele frequencies, even after stratifying the SARS-infected group into severe and mild cases. Xiong et al. [6] did not find any significant association either (after correction for multiple tests) with HLA-A, HLA-B and HLA-DRB1 alleles in a case-control study involving 95 SARS recovered patients and 403 healthy controls from Guangdong, China. Some results were also reported for HLA-C: Chen et al. [7] concluded that allele HLA-C*08:01 was a SARS susceptibility marker after comparing 20 SRAS seropositive patients with 80 controls in Taiwan, and Wang et al. [8] found that both HLA-C*15:02 and HLA-DRB1*03:01 were significantly associated and protective to the disease (as previously suggested by Ng et al. [4] for HLA-DRB1*03:01) by comparing 56 SARS-positive to 41 SARS-negative healthcare workers, also in Taiwan. In these two studies, however, corrections for multiple tests were not reported. One association that remained significant after multiple test correction, found by Keicho et al. [9], was between HLA-DRB1*12:02 and SARS development (i.e., progress of the disease) when 44 SARS patients were compared with both 101 controls who had close contacts with patients and 50 healthy individuals who did not have any contact history, all Vietnamese. The association was less strong, however, after moving 16 individuals who were later found to be infected from the control to the case group. All the associations summarised above are reported in detail in table 1.

As we note, several efforts were made to identify HLA susceptibility or protective factors to SARS-CoV-1 after the first SARS epidemic that broke out in East Asia in 2002−2003, although most studies provided weak or conflicting results needing further validation. In our view, this should not discourage research groups from undertaking such studies in relation to the new SARS-CoV-2 virus, but because of the high level of HLA polymorphism special care has to be taken on the study design, namely the sample sizes and composition of case and control groups. Moreover, the fact that we are facing, for the first time in human history, a pandemic affecting nearly all countries of the world at the same time might be an opportunity to coordinate such efforts at the international level in order to take the global population stratification into account.

## Bioinformatic and experimental studies

Another kind of approach that clearly emerged from our review of the literature regarding HLA and SARS is the search for virus-derived immunogenic peptides that would be presented by HLA molecules and would thus act as CD4+ B cell and/or CD8+ T cell epitopes. The identification of such peptides would indeed help to better understand the immune responses to SARS viruses and promote the development of peptide-based specific vaccines, as pursued by the Human MHC Project [10].

Again, most studies published to date still relate to SARS-CoV-1 (table 2). Sylvester-Hvid et al. [11] used a combination of bioinformatics and immunological approaches to predict and validate HLA binding to selected SARS-CoV-1 derived peptides. Eight functional groups, defined as supertypes, of HLA-A (i.e., A1, A2, A3, A24) and HLA-B (i.e., B7, B44, B58, B62) alleles were used for the analysis. For each of them, the binding of a list of peptides was both predicted and validated, providing crucial information for vaccine design. From the point of view of HLA variation, a relevant result was that most viral peptides appeared to be good binders to different HLA proteins of the same functional group (e.g., A*03:01 and A*11:01). It suggests that good peptide coverage can be achieved by many different combinations of HLA alleles, given that proteins of different functional groups are present in a population. Blicher et al. [12] investigated the X-ray crystallographic structure of the specific binding between one HLA-molecule, HLA-A*11:01, and a nonameric SARS nucleocapsid (N) peptide. A*11:01 was chosen for this study for two reasons: first, it appeared to influence the control of several viruses, namely human immunodeficiency, Epstein-Barr and hepatitis B viruses; and second, its frequency was high (up to 27%) in populations from East Asia where the SARS-CoV-1 epidemic first broke out in 2002. The peptide was chosen among the set of best and confirmed HLA Class I binding peptides of SARS-CoV-1 proposed by Sylvester-Hvid et al. [11] (mentioned above) and the fact that it had a high probability of being generated by proteasomal processing and further translocated into the endoplasmic reticulum to be presented by HLA. It revealed a relatively good binding to A*11:01 ($IC_{50}$ of 70 nM). As it was conserved across different SARS-CoV-1 strains by assuming diverse functions, it was considered as a putative candidate in the development of a peptide-based vaccine. The authors also stressed the fact that the HLA-A*11 structure was very similar to that of other molecules of the same supertype, namely A*68, possibly also A*03, A*31 and A*33, and key peptide residues for T cell receptor (TcR) interactions were determined. Tsao et al. [13] carried out binding predictions between HLA-A*02 molecules and peptides derived from nucleocapsid (N) and spike (S) SARS-CoV-1 proteins. Several such peptides were then synthetised and used in binding assays to validate binding affinities. They identified three N-specific and two new (relative to three previously discovered) S-specific peptides as HLA-A*02:01-restricted cytotoxic T lymphocyte epitopes of SARS-CoV-1 N and S proteins, respectively. A novel HLA-A*02:01 epitope of the SARS-CoV-1 N protein was further identified by Cheung et al. [14]. Rivino et al. [15] evaluated the reliability of predictive bioinformatic algorithms to identify CD8+ T cell epitopes in individuals of Asian origin infected with different viruses among whom were five patients with SARS-CoV-1. Although this study highlighted the limitations of such algorithms, the predictions were successful for peptides of SARS-CoV-1, as the predicted HLA

**Table 1:** Case-control studies testing putative associations between HLA alleles and SARS-CoV-1 disease after the first SARS epidemic that broke out in 2002–2003.

| Region | Loci tested | Number of cases | Number of controls | HLA Allele | OR | p-value (susceptibility) | p-value (protection) | Significance after correction for multiple testing | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Taiwan | HLA-A, HLA-B, HLA-DRB1 | 33 probable SARS patients | 101 (Control A)* | HLA-B*46:01 | 2.08 | 0.04 | – | n.s. | Lin et al. 2003 [2] |
| | | 33 probable SARS patients | 190 (Control B)† | HLA-B*46 | 1.86 | n.s. | – | – | |
| | | 6 severe cases (among the 33) | 101 (Control A) | HLA-B*46:01 | 10.62 | 0.0008 | – | 0.0279 | |
| | | 33 probable SARS patients | 101 (Control A) | HLA-B*54:01 | 5.44 | 0.02 | – | n.s. | |
| | | 33 probable SARS patients | 190 (Control B) | HLA-B*54 | 1.99 | n.s. | – | – | |
| | | 6 severe cases (among the 33) | 101 (Control A) | HLA-B*54:01 | NA | n.s. | – | – | |
| | | 33 probable SARS patients | 101 (Control A) | HLA-B*39:01 | 2.68 | n.s. | – | – | |
| | | 33 probable SARS patients | 190 (Control B) | HLA-B*39 | 3.81 | 0.03 | – | n.s. | |
| | | 6 severe cases (among the 33) | 101 (Control A) | HLA-B*39:01 | NA | n.s. | – | – | |
| | | 33 probable SARS patients | 101 (Control A) | HLA-B*13:01 | 0.16 | – | 0.03 | n.s. | |
| | | 33 probable SARS patients | 190 (Control B) | HLA-B*13 | 0.16 | – | 0.02 | n.s. | |
| Taiwan | HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1 | 20 seropositive patients | 80 seronegative | HLA-C*08:01 | 3.4 | 0.003 | – | NA | Chen et al. 2006 [7] |
| Taiwan | HLA-A, HLA-B, HLA-C, HLA-DRB1 | 56 confirmed patients | 41 healthy negative | HLA-C*15:02 | 0.17 | – | 0.01 | NA | Wang et al. 2011 [8] |
| | | | | HLA-DRB1*03:01 | 0.3 | – | 0.04 | NA | |
| Hong Kong | HLA-A, HLA-B, HLA-DRB1, HLA-DQB1 | 83 serologically confirmed | 18,774 unrelated BMD | HLA-B*07:03 | 4.08 | 0.00072 | – | <0.0022 | Ng et al. 2004 [3] |
| | | 79 serologically confirmed | 250 unrelated BMD | HLA-DRB1*03:01 | 0.06 | – | 0.00008 | <0.0042 | |
| | | 90 serologically confirmed | 250 unrelated BMD | HLA-DQB1*06:01 | 2.12 | 0.0095 | * | n.s. | |
| Hong Kong | HLA-A, HLA-B, HLA-C, HLA-DRB, HLA-DQA1, HLA-DQB1 | 102 serologically confirmed | 108 close contacts‡ | HLA-DRB4*01:01:01:01 | 2.36 | 0.0031 | – | n.s. | Ng et al. 2010 [4] |
| | | | | HLA-B*15:02 | 0.31 | – | 0.0037 | n.s. | |
| | | | | HLA-DRB3*03:01:01 | 0.45 | – | 0.0282 | n.s. | |
| Hong Kong | HLA-A, HLA-B, HLA-DRB1 | 176 mostly serologically confirmed | 18,774 typed for class I, 250 typed for class II unrelated BMD | – | – | n.s. | n.s. | – | Yuan et al. 2014 [5] |
| | | 128 mild cases (among the 176) | | – | – | n.s. | n.s. | – | |
| | | 48 severe cases (among the 176) | | – | – | n.s. | n.s. | – | |
| Guangdong, China | HLA-A, HLA-B, HLA-DRB1 | 95 serologically confirmed | 403 healthy | HLA-A*23 | 21.58§ | 0.0361 | n.s. | n.s. | Xiong et a. 2008 [6] |
| | | | | HLA-A*34 | 21.58§ | 0.0361 | – | n.s. | |
| | | | | HLA-B*58 | 0.49 | – | 0.027 | n.s. | |
| | | | | HLA-B*60 | 1.93 | 0.0061 | – | n.s. | |
| | | | | HLA-B*61 | 0.19 | – | 0.0176 | n.s. | |
| | | | | HLA-DRB1*12 | 1.64 | 0.046 | – | n.s. | |
| Vietnam | HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1 | 44 SARS patients | 101 close contacts‡ | HLA-DRB1*12:02 | NA | 0.0032 | – | 0.042 | Keicho et al. 2009 [9] |
| | | | 50 not close contacts | HLA-DRB1*12:02 | NA | 0.0053 | – | NA | |
| | | 60 infected SARS patients¶ | 85 non-infected¶ | HLA-DRB1*12:02 | NA | 0.0231 | – | NA | |

BMD = serologically typed bone marrow donors; n.s. = not significant; NA = not available; OR = odds ratio * Control A = 101 high risk non infected health care workers; † Control B = 190 healthy unrelated Taiwanese; Control B only tested by serological typing for HLA-A and HLA-B; BMD: ‡ close contacts = subjects who had close contacts with SARS patients; § for A*23 and A*34, the high OR values correspond to 2 cases and 0 controls; ¶ 16 close contacts further found to be infected were moved to the case group.

restriction was concordant with the experimental HLA restriction for six out of seven N protein peptides (4 HLA-B*40:01, 1 HLA-B*55:02 and 1 HLA-B*15:25 restrictions). Interestingly, Zhang [16] designed a novel *in silico* approach for the identification of HLA class I T cell epitopes through epitope prediction models in combination

with molecular docking techniques (3D structural modelling of peptide-HLA-TcR complex) and applied it to predict T cell epitopes in SARS-CoV-1 S, N and M proteins (the major structural proteins of SARS-CoV-1), with 90% accuracy (correlation with experimental data) for S protein.

A few works aiming at identifying SARS-CoV-2-derived immunogenic peptides that would be good candidates for vaccine development were also published recently (table 2). Lee and Koohy [17] identified a set of peptides that were (i) identical to SARS-CoV-1 peptides that had previously been listed as immunogenic by T cell assays – these 28 peptides were shown to bind several HLA class I (mostly HLA-A*02:01, but also HLA-B*40:01) and class II (mostly HLA-DRB1*04:01, but also HLA-DRA*01:01/DRB1*07:01) molecules; (ii) highly similar to immunogenic peptides reported in the Immune Epitope Database (IEDB), which corresponded to 48 different peptides among which 22 displayed higher immunogenicity scores than IEBD peptides; and (iii) both strong binders to common HLA alleles in Chinese and European populations (HLA-A*02:01, HLA-A*01:01, HLA-B*07:02, HLA-B*40:01 and HLA-C*07:02) and potentially recognised by T cell receptors with high immunogenicity scores, two conditions that were fulfilled by 63 peptides. This shortlist of peptides is proposed by the authors for experimental validation. Another relevant paper was published by Ahmed et al. [18], who combined experimental, *in silico* and populational approaches. Based on previous knowledge, the authors first identified experimentally determined SARS-CoV-1 derived T cell epitopes in the immunogenic structural spike (S) and nucleocapsid (N) proteins of SARS-CoV-1 that were associated with positive T cell or HLA binding assays, based on the high genetic similarity between the two viruses. A number of SARS-CoV-1 derived epitopes were found to map identically to SARS-CoV-2 proteins. Then, based on the HLA alleles that positively bound these epitopes and their frequencies in human populations, the authors provided a subset of epitopes that maximised the global population coverage (i.e., the number of individuals that were likely to elicit an immune response to at least one epitope of the set) to help guide efforts to develop a vaccine. HLA binding assays were performed for 19 epitopes that displayed positive T cell assays in all retrieved SARS-CoV-2 proteins, resulting positive for five distinct alleles, HLA-A*02:01, HLA-B*40:01, HLA-DRA*01:01, HLA-DRB1*07:01 and HLA-DRB1*04:01. The population coverage of these alleles was moderate: 59.76% globally and low for China (32.36%). By expanding this set of epitopes to those displaying positive HLA binding assays but unknown T cell assays, a total of 102 epitopes derived from S or N proteins would be associated to a set of 20 HLA alleles providing a global coverage of 96.29%. However, the immunogenicity of these epitopes remains to be tested, and this approach also needs a better integration of HLA population genetics as this study does not take into account population structure in the distribution of HLA alleles at different loci.

**Table 2:** HLA-related bioinformatic and experimental studies carried out to determine SARS-CoV-1 / CoV-2 immunogenic epitopes for vaccine design.

| Study | Virus | Bioinformatic approach | Experimental approach | Main conclusions |
|---|---|---|---|---|
| Sylvester-Hvid et al. 2004 [11] | SARS-CoV-1 | Peptide-binding predictions between 9 HLA supertypes (A1, A2, A3, A24, B7, B44, B58, B62) and all possible nonamers of the SARS-CoV-1 proteome: ~10,000 predictions per supertype. | HLA biochemical binding validation assays for the 15 top-ranking nonamers of each supertype: 94% of (either positive or negative) predictions confirmed. | Each HLA supertype binds a specific set of peptides with few overlap (2–3%); each peptide binds different HLA molecules of the same supertype with extended overlap. |
| Blicher et al. 2005 [12] | SARS-CoV-1 | Choice of one specific peptide (KTFPPTEPK) of the SARS-CoV-1 nucleocapsid (N) protein (N362–370 peptide) among the best confirmed binders reported by Sylvester-Hvid et al. [11]. | X-ray crystallography of the N362–370 peptide in complex with protein HLA-A*1101; the peptide is expected to bind several members of the A3 supertype (e.g., A68) showing similar structures. | Key amino acid positions for HLA peptide-binding and T cell receptor interactions are determined through this structural approach and useful for vaccine development. |
| Tsao et al. 2006 [13]; Cheung et al. 2007 [14] | SARS-CoV-1 | Peptide-binding predictions between the HLA-A*0201 molecule and nonamer peptides of the nucleocapsid (N) and spike (S) SARS-CoV-1 proteins. | Peptide-binding affinity validation through T2-cell binding assays and other experimental approaches (transgenic mice and *in vitro* human peripheral blood mononuclear cell vaccinations) to validate immunogenicity. | Several N-specific (N223–231, N20–N228, N227–235, and N317–325) and S-specific (S787–795 and S1042–1050) putative cytotoxic T lymphocyte epitopes are to be considered in peptide-based vaccine development. |
| Rivino et al. 2013 [15] | SARS-CoV-1 | Peptide-binding and immunogenicity predictions between HLA-A*1101 and A*2402 molecules (frequent in Southeast Asia) and peptides of the 3a and nucleocapsid (N) SARS-CoV-1 proteins. | HLA biochemical binding validation assays and immunogenicity testing in SARS patients (Asian) cell lines of the predicted epitopes; parallel identification of cytotoxic T lymphocyte epitopes by traditional approaches (T cell cultures) and comparisons. | Evaluation of the predictive power of bioinformatic algorithms through comparisons with experimental data; unlike for other viruses tested (dengue and hepatitis B), the results are satisfactory for SARS-CoV-1. |
| Zhang 2013 [16] | SARS-CoV-1 | Design of a novel computational approach combining peptide-binding predictions with molecular docking (3D structural modelling of peptide interactions with HLA and Tcell receptor) techniques. | Evaluation of the methodology through comparisons of predicted HLA-A*0201-restricted peptides of the nucleocapsid (N), membrane (M) and spike (S) SARS-CoV-1 proteins with experimentally-determined epitopes: 90% accuracy for S protein epitopes. | The combination of several complementary bioinformatic approaches increases the power of identifying T cell epitopes and may reduce the number of peptides required for experimental assays. |
| Lee and Koohy 2020 [17] | SARS-CoV-2 | Peptide-binding and immunogenetic predictions for SARS-CoV-2 derived peptides used to propos e a list of peptides binding common HLA alleles in Chinese and European populations and having high T cell receptor recognition potential. | Comparisons with SARS-CoV-1 immunogenic peptides previously identified by experimental T cell assays or already recorded as immunogenic in the IEBD database used to propose additional lists of SARS-CoV-2 epitopes. | Relevant information acquired through previous SARS-CoV-1 epitope studies and the use of various predictive bioinformatic tools allows determining an extensive list of candidate SARS-CoV-2 epitopes for peptide-based vaccine design. |
| Ahmed et al. 2020 [18] | SARS-CoV-2 | Peptide-binding and immunogenetic predictions for SARS-CoV-2 derived peptides and population coverage analysis of the associated HLA alleles. | Identification of SARS-CoV-2 B cell and T cell epitopes derived from the spike (S) and nucleocapsid (N) proteins through comparisons with experimentally-determined SARS-CoV-1 immunogenic peptides. | An extensive list of epitopes determined through both *in silico* predictive tools and comparisons with previous knowledge on SARS-CoV-1 immunogenic peptides is suggested to provide a broad population coverage useful for vaccine development. |

## Concluding remarks

Although both genetic and non-genetic (environmental) factors are certainly expected to influence the susceptibility to or protection against the new coronavirus SARS-CoV-2 of individuals, the crucial role played by HLA molecules in the immune response – in particular through pathogen-derived peptide presentation – and the huge molecular variability of HLA alleles in human populations call for thorough studies aiming at exploring the role of HLA genotypes on individual responses to SARS-CoV-2 infection and/or progression. Besides case-control studies, which might help in identifying associated markers provided that the research plan is carefully designed, *in silico* HLA peptide-binding predictions combined with experimental HLA binding and T cell response assays appear to be very promising for vaccine development. We are convinced that the HLA community, which is most active in International HLA and Immunogenetics Workshops (IHIW) and other extended networks, such as the European Federation for Immunogenetics (EFI), will share its efforts to untangle the secrets of the new SARS-CoV-2 pandemic and alleviate its dramatic effects on human populations.

**Acknowledgments**

The author's research is supported by the Swiss National Science Foundation (grants #31003A_144180 and #310030_188820). We also thank José Manuel Nunes for amending the first draft of this manuscript.

**Disclosure statement**

No financial support and no other potential conflict of interest relevant to this article was reported.

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